REMARKS

Status of the Claims

Claims 17-25, 28, 31-39 and 41-55 are pending. Claims 17-24, 31-39 and 41-55 are withdrawn from consideration as being drawn to a non-elected invention. Claims 26-27, 29, 30 and 40 are cancelled. Claims 25 and 28 are currently pending. Claim 25 is amended. No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Amendments to the claims

Claim 28 is amended to overcome the rejection under 35 U.S.C. 102(e). No new matter has been added.

The 35 U.S.C. §102 rejections

Claims 25 and 28 remain rejected under 35 U.S.C. 102(e) as being anticipated by Pollak *et al.* (U.S. 6,645,770, 1998). Applicants respectfully traverse the Examiner's rejection.

The Examiner states that the present claims are anticipated by Pollak because of the technical reasoning that necessarily flows from the teachings in Pollak; that is, the active steps of measuring IGF-I, IGFBP-3 and PSA levels, calculating a ratio based on at least two of the measured concentrations, and using the ratio to predict prostate cancer and/or differentiating cancer from other prostatic diseases, such as benign prostatic hyperplasia, thus establishes a nexus between prostate cancer and high levels of IGF-I with high PSA levels. Additionally, the Examiner states that the present claims do not

differ from Pollak because the presently claimed methods do not contain the limitation that the individual already has a prostate disorder or prostate cancer.

Applicants respectfully traverse the Examiner's rejection, because the teachings of Pollak are limited to using measurements of IGF-I, IGFBP-3, and PSA only to predict a risk of future onset of prostate cancer in an individual having no history of prostate cancer, as opposed to the risk of the onset of another prostatic disorder or another type of cancer. In contrast, the present claims as amended describe methods to distinguish between a prostate disorder and prostate cancer in an individual having a prostate disorder or prostate cancer.

Claim 25 has been amended to recite a diagnostic method for discriminating between benign prostate disorders and prostate cancer in an individual having a prostate disorder or prostate cancer by calculating a ratio based on at least two of the measured concentrations of IGF-I, IGFBP-3, and PSA. Therefore, the present claims are clearly distinguished from the teachings of Pollak, because in Pollak all measurements of IGF-I, IGFBP-3, and PSA were taken from individuals with no history of cancer.

The Examiner agrees with the Applicant that Pollak does not teach any specific examples of measuring IGF-I, IGFBP-3, or PSA levels in individuals with existing cancer, but states that the methods of the present claims necessarily flow from the teachings in Pollak, in that Pollak establishes a link between prostate cancer and high levels of IGF-I levels with high PSA levels.

The Applicant respectfully argues that the link that Pollak establishes between prostate cancer and high IGF-I and PSA levels is one that is predictive of the risk of future onset of prostate cancer only. The subjects in the Pollak study, from which all measurements were taken, had no history of cancer, except for non-melanoma skin cancer (column 6, lines 19-23); the IGF-I and IGFBP-3 levels were measured using blood

samples that were drawn an average of seven years prior to cancer diagnosis (column 11, lines 54-57). High levels of IGF and/or low levels of IGFBP were correlated with increased risk of eventually developing prostate cancer (column 1, lines 30-32, Tables 1 and 2). Pollak also describes analyses of the IGF-I levels compared to the future occurrence of high grade versus low grade cancer at diagnosis (column 8, lines 42-47), but found no significant association between IGF-I and risk of developing high grade/stage versus low grade stage prostate cancer (column 10, lines 36-44). Thus, Pollak does not teach that IGF-I levels can predict the risk of developing a low grade versus a high grade prostate cancer.

Pollak describes the measurement of IGF-I status combined with PSA measurements to predict the risk of subsequent prostate cancer (Example 2, columns 10-11). Higher IGF-I levels adjusted for IGFBP-3 also had a strong relation to risk of developing prostate cancer, regardless of PSA levels (column 11, lines 10-26, and Table 3). Thus, by using Pollak's methods a risk of future prostate cancer can be detected in individuals with no sign of cancer, including individuals with a PSA level in the normal range. Any prediction of prostate cancer based on PSA levels is also predictive of the risk of future onset of prostate cancer only. Thus, the teachings of Pollak are to use IGF-I, IGFBP-3 and PSA measurements in subjects without any evidence of prostate disease, to predict the risk of occurrence of prostate cancer in the future. Pollak contains no teaching of methods to measure IGF-I, IGFBP-3 or PSA in individuals having a prostate disorder or prostate cancer, in order to distinguish a prostate disorder from prostate cancer in the individual.

Pollak makes the statement that the method therein is most preferably used to determine the risk of an individual developing prostate cancer, diagnosing prostate cancer or assessing the progress of the cancer; and that accordingly, the method therein may be

useful in predicting prostate cancer, differentiating cancer from other prostatic diseases (column 5, lines 8-18). The Applicant respectfully argues that the teachings in Pollak can be only be used in the sense of "differentiating cancer from other prostatic diseases" in that Pollak's methods may be used to predict whether an individual is more likely to eventually develop prostate cancer compared to a different prostatic disorder such as prostatic hyperplasia. Any differentiation between prostate cancer and other prostatic diseases is one of prediction of the likelihood of future occurrence of prostate cancer versus another prostatic disorder only. With only measurements of IGF-I, IGFBP-3 and PSA levels in samples from individuals with no cancer, it is not possible to distinguish between different prostatic conditions that do not yet exist, because it is uncertain how these levels will be altered because of the onset of the condition or due to other factors. For example, Pollak refers to a study in which IGF-I levels were measured in men already diagnosed with prostate cancer and healthy controls (column 12, lines 6-19). This study showed a positive association between IGF-I levels and prostate cancer risk of borderline significance; however, Pollak states that the retrospective design used in that study could not rule out an effect of the cancer, or its treatment, on IGF-I levels. This statement suggests that measurements of IGF-I levels in individuals will be affected by the presence of prostate cancer and by any treatments for the cancer, and accordingly that distinguishing between the risk of developing future prostate cancer versus another prostatic condition using IGF-I levels will be uncertain where there is existing prostate cancer. Pollak therefore teaches away from using the methods described therein in cases where there is existing prostate cancer. Pollak provides no teaching that the measurement of IGF-I levels, as well as IGFBP-3 and PSA levels, can distinguish between existing prostate cancer and other prostate disorders.

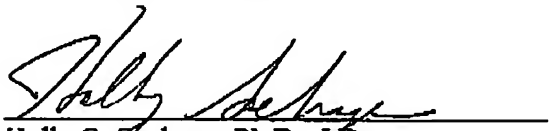
In contrast to the teachings in Pollak, the present claims describe methods to discriminate between benign prostate disorders and prostate cancer in an individual already having such a disorder or cancer, by calculating an indicator ratio based on at least two of the measured concentrations of either IGF-I, IGFBP-3, and PSA in a sample from that individual. As described in the present specification, the presently claimed methods are useful to distinguish between the presence of malignant versus benign prostate disorders in individuals having serum levels of PSA in the "gray-zone" range of about 4-10 μg/L (page 2, lines 21-24 and page 3, lines 1-8), whereas an individual with highly elevated PSA (e.g., 20-50 mg/L) would be most likely diagnosed as having prostate cancer. The measurements of IGF-I and IGFBP-3 and calculation of the claimed ratios thus provide methods to more accurately determine whether an elevated PSA in the "gray zone" range is due to the presence of a malignant prostate disease state or other conditions such as benign prostatic hyperplasia, and thus to better determine the proper course of treatment in patients (page 9, lines 15-20). In Example 1 of the present specification, samples from patients with confirmed prostatic disease were selected to have a total PSA level in the diagnostic gray-zone range, in order to demonstrate that measurements of the IGF-I status provide methods to enhance the ability to discriminate between benign prostatic hyperplasia and prostate cancer in these patients (Example 1). In contrast, Pollak teaches that IGF-I status was strongly associated with the risk of developing future prostate cancer, regardless of the PSA levels (Example 2, columns 10-11 and column 11, lines 26-31). The methods in Pollak only teach the measurement of IGF-I, IGFBP-3, and PSA in individuals with no history of cancer, so that these methods cannot be used to distinguish between existing prostate cancer and other prostate disorders.

The teachings of Pollak only provide methods to predict the future development of prostate cancer, and do not teach any method to discriminate between a benign prostate disorder and prostate cancer in and individual having such a prostate disorder or prostate cancer. Therefore, Pollak does not teach each and every limitation in the present claims as amended, and accordingly does not anticipate the present claims. Accordingly, Applicants respectfully request that the rejection of claims 25 and 28 under 35 U.S.C. 102(e) be withdrawn.

This is intended to be a complete response to the Office Action mailed July 26, 2005. If any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned for immediate resolution.

Respectfully submitted,

Date: October 26, 2005



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